Medical Considerations for Moms

Prevention Branch, Division of Viral Hepatitis

Perinatal Hepatitis B and
HIV Grantees Meeting
Atlanta
April 30-May 2, 2002

CDC

Treatment of Chronic Hepatitis B

Goals

- Suppress HBV replication
- Decrease hepatic necroinflammation and fibrosis
- Prevent progression to cirrhosis, liver failure and HCC

Who Should be Treated?

- All HBV carriers are potential treatment candidates
- Persons not treated now need monitoring
- A patient who is not a treatment candidate now can be a treatment candidate in the future
  - Changes in HBV replication status and/or activity/stage of liver disease
  - Availability of new and better treatments

Who Should be Treated?

- Medical evaluation includes
  - History and physical
  - CBC, plts, LFT, INR
  - HBeAg, HBV DNA
  - Anti-HCV, anti-HDV, Anti-HIV
  - AFP or ultrasound for HCC screening
  - Liver biopsy if indicated

What About Infected Children?

- Infected children need medical evaluation
- Drug options are more limited
  - Interferon
  - Lamivudine
  - Clinical trials for adefovir

Who Should be Monitored?

- All HBsAg+ persons who are not treatment candidates need follow-up:
  - Regular ALT tests
  - HBV DNA
  - AFP or ultrasound for HCC screening
    - Every 6-12 months with high ALT/DNA
  - HBeAg+ patients need more frequent visits

Source: Lok A, McMahon B. Chronic hepatitis B (AASLD Practice guidelines). www.aasld.org

Hepatitis B Medications

Drug	Treatment course	Side effects
Interferon-alpha (Intron A, 1991)	**6 months – 1 year**	**Fever, aches, depression, headache**
Pegylated Interferon (Pegasys, 2005)	**6 months – 1 year**	**Fever, aches, depression, headache**
Lamivudine (Epivir-HBV, Zeffix, or Heptodin, 1998)	**≥1 year**	**Resistance**
Adefovir dipivoxil (Hepsera, 2002)	**≥1 year**	**Renal effects**
Entecavir (Baraclude, 2005)	**≥1 year**	**?**
Telbivudine (Tyzeka, Sebivo, 2006)	**≥1 year**	**?**

Treatment in Pregnancy?

- Lamivudine may reduce mother-to-infant transmission in the presence of high DNA titers[1,2]
  - High rates of lamivudine resistance develop (14%-32% in 1 year, 60%-70% in 5 years)

1. van Zonneveld M et al. Lamivudine treatment during pregnancy to prevent perinatal transmission of hepatitis B virus infection. J Viral Hepat. 2003;10:294-297.
2. Xu W-M et al. Efficacy and safety of lamivudine in late pregnancy for the prevention of mother-child transmission of hepatitis B: a multicentre, randomised, double-blind, placebo-controlled study [abstract 246]. Hepatology. 2004;40(suppl 1):272A.

Hepatitis B Drugs in Trials

Nucleoside Analogues - Interfere with viral DNA polymerase enzyme used for hepatitis B virus reproduction		
Emtricitabine (FTC)	Inhibits viral DNA polymerase	Phase III
Clevudine (L-FMAU)	same	Phase III, South Korea; Phase III, US (2006)
Viread (Tenofovir)	same	Phase III
Valtorcitabine (monoval LdC)	same	Phase II
Amdoxovir (DAPD)	same	Phase II
ANA 380 (LB80380)	same	Phase II
Pradefovir (Remofovir)	same	Phase II
RCV (Racivir)	same	Phase II
Non-Nucleoside Antivirals - Interfere with proteins involved in viral reproduction		
NOV-205 (BAM 205)	Small Molecule	Approved in Russia
HepeX-B (XTL-001)	Human monoclonal antibodies	Phase II/III; Orphan drug approval in US for liver cancer
Nitazoxanide (Alinia)	Small Molecule	Phase II Egypt
UT 231-B	Small Molecule	Preclinical HBV (Phase II HCV)
Bay 41-4109	Inhibits viral nucleocapsid	Preclinical
Non-Interferon Immune Enhancers - Boost T-cell infection-fighting immune cells and natural interferon production		
EHT899	Oral Viral Protein	Phase II Israel
Zadaxin (Thymosin alpha-1)	Immune stimulator	Orphan drug approval in US for liver cancer
Hi-8 HBV	Therapeutic HBV Vaccine	Phase II
HepaVaxx B	Therapeutic HBV Vaccine	Phase I
HBV Core Antigen Vaccine	Therapeutic HBV Vaccine	Phase I
SpecifEx-HepB	Immunological Cell Transfer	Preclinical/Phase I
HepX	Expressed Interfering RNA	Preclinical

Treatment Adjuncts

HBsAg+ pregnant women should be advised to:

- Discuss the risk for transmission and the need for testing and vaccination with household contacts, sex partners, and needle-sharing contacts
- Use condoms until sex partners are immune to HBV infection
- Visit their regular medical doctor at least annually
- Get vaccinated against hepatitis A
- Abstain from alcohol use
- Not share any personal items that may have blood on them (e.g., toothbrushes and razors).

Pregnancy as an Opportunity

- Pregnancy-related Medicaid available in most states will cover medical evaluation of HBV-infected mothers (until 60 days postpartum)

- Many states include undocumented internationals in pregnancy-related Medicaid eligibility

Other Considerations in Pregnancy?

Amniocentesis?

The risk of fetal hepatitis B infection through amniocentesis is low.

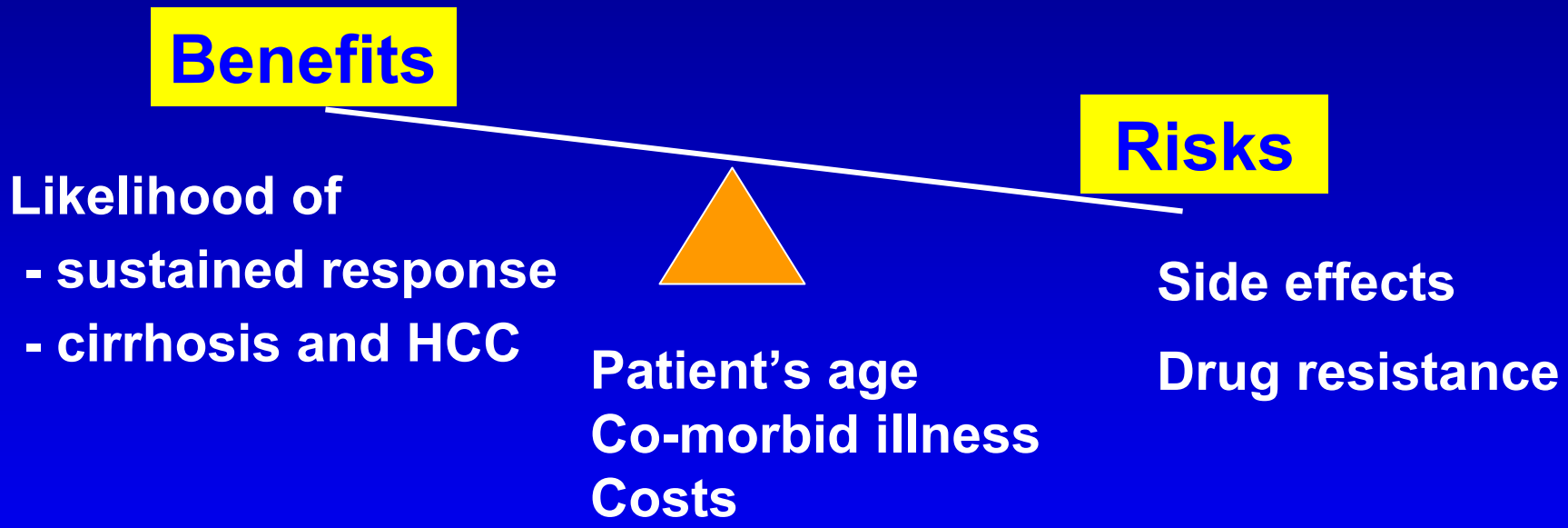
C-Section?

The mode of delivery does not appear to have a significant effect on the interruption of HBV maternal-baby transmission. Delivery by cesarean section for the purpose of reducing transmission is not recommended by either the CDC or the ACOG.

Breast feeding?

With appropriate hepatitis B immunoprophylaxis, breast-feeding poses no additional risk for transmission

When to start treatment?



Likelihood of cirrhosis / HCC in the next 10-20 yrs

Likelihood of sustained viral suppression after a defined course of treatment

Virologic Responses

Achievement of virologic response is not an indication to stop treatment

- Decrease in serum HBV DNA
  - Preferably to undetectable by PCR
  - IFN: HBV DNA frequently detectable at the time of HBeAg loss
  - NA: HBV DNA may have been undetectable for yrs yet HBeAg still positive
- HBeAg loss
  - Applicable to HBeAg+ patients only
  - Not clear if HBeAg seroconversion confers greater durability
- HBsAg loss
  - Ultimate goal
  - More likely after IFN than NA Rx
  - Rare among Asian patients

Management of Hepatitis B – Key Points

- Hepatitis B is preventable
  - Screen, and vaccinate babies and at-risk moms
- HBV persists for life and the course of chronic HBV infection is highly variable
  - All HBsAg+ persons should be monitored for life
- Hepatitis B is treatable
  - Identify and treat those who are most likely to benefit
  - Monitor others and treat when indicated

Resources

www.aasld.org

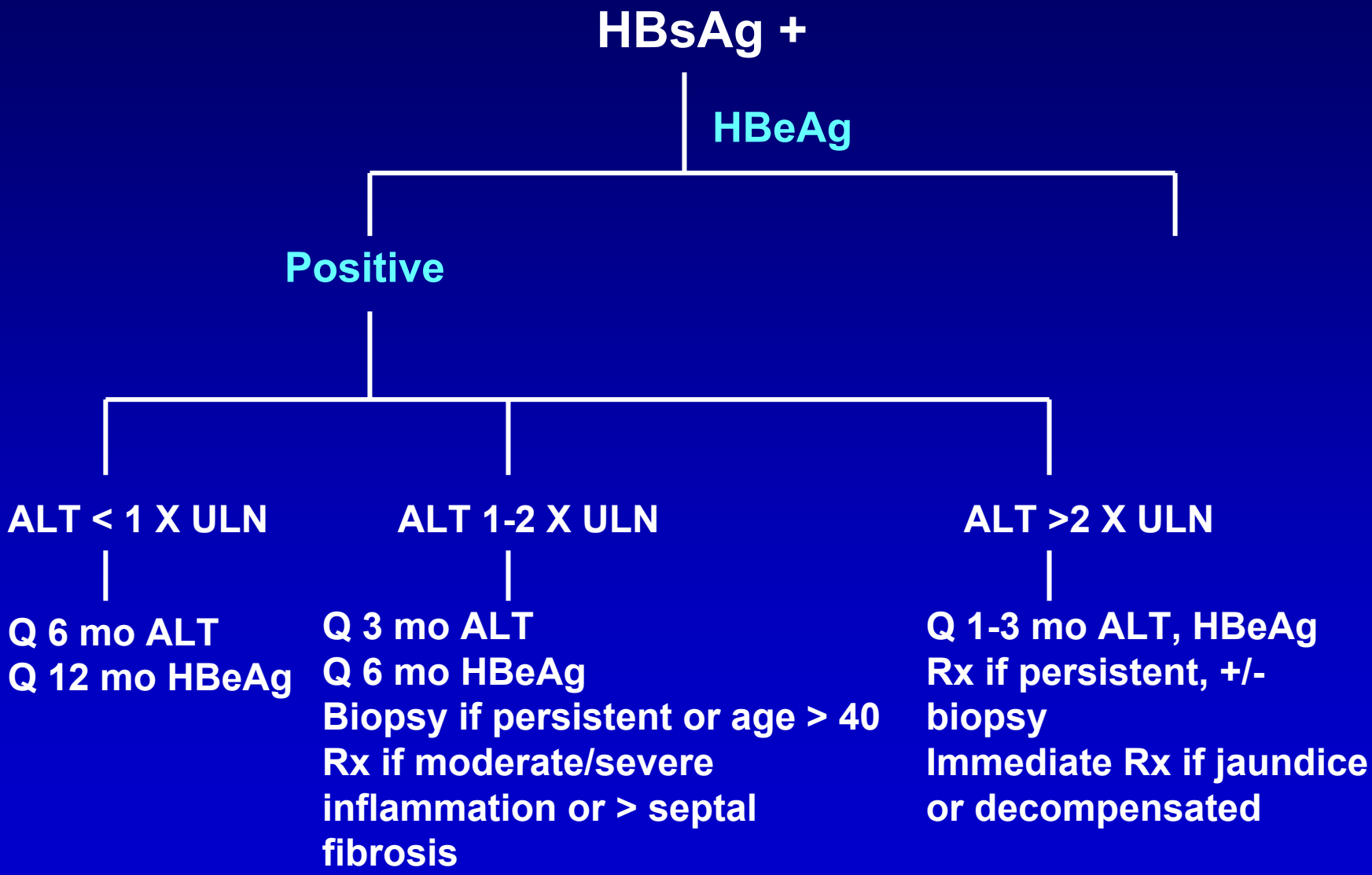
www.act-hbv.com

www.hepb.org

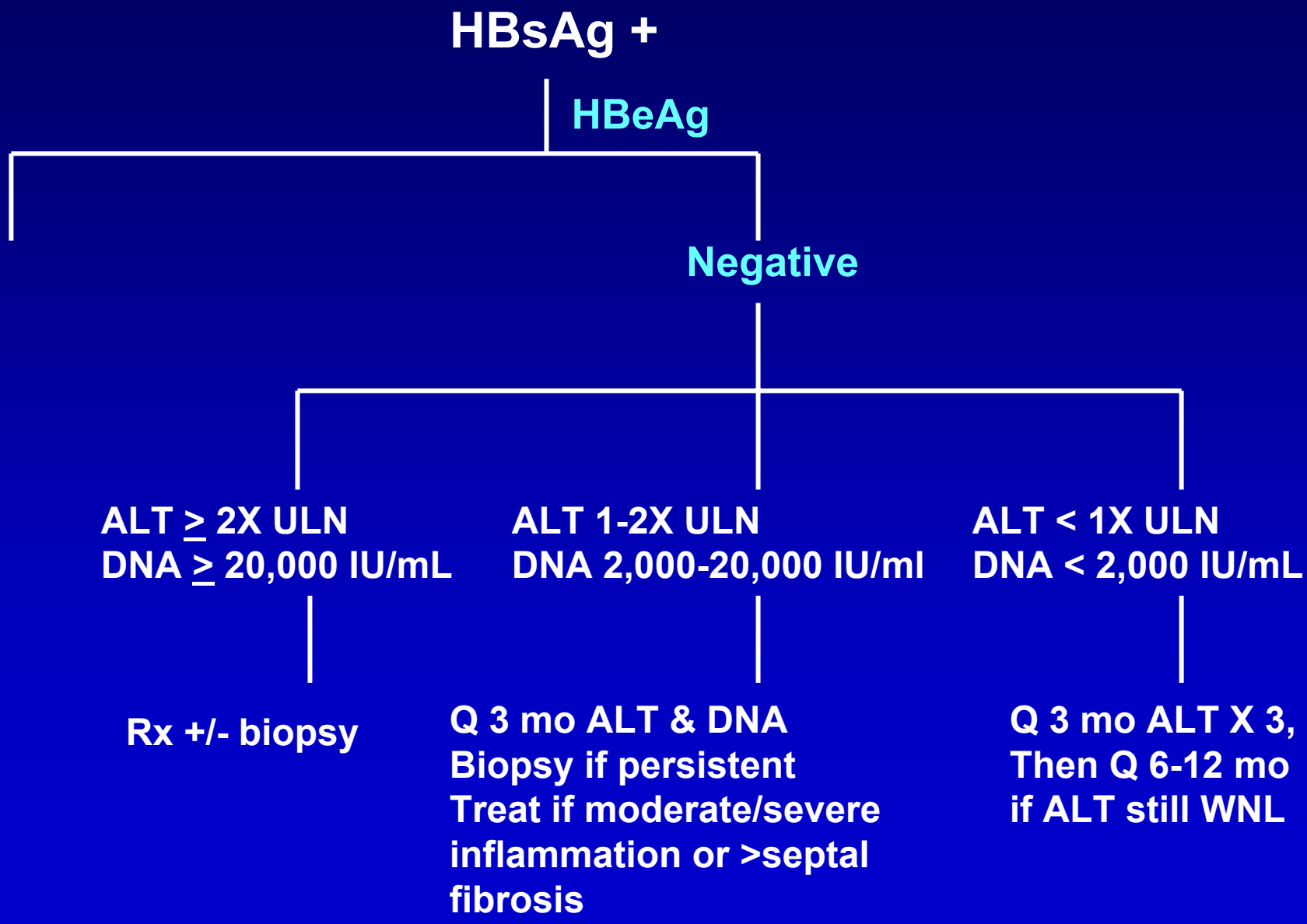
Thanks

Disclaimer: The findings and conclusions in this presentation have not been formally disseminated by CDC and should not be construed to represent any agency determination or policy

Treatment of Chronic Hepatitis B



Treatment of Chronic Hepatitis B



Virologic Response after 1 year Treatment

	PegIFN	Nucleos(t)ide analogues
HBeAg+ patients		
Undetectable HBV DNA	25%	21-67%
HBeAg seroconversion	27%	12-22%
Durability of response	~90%[a]	~80%[b]
HBeAg- patients		
Undetectable HBV DNA	63%	51-90%
Durability of response	~20%	<10%

[a] Additional patients seroconvert after IFN is stopped

[b] Treatment continued for ≥ 6 ms after HBeAg seroconversion

Rates of antiviral-resistant HBV mutations reported in clinical trials

Antiviral therapy	Rates of genotypic resistance
Nucleoside-naïve pts	
Lamivudine	15-30% after 1 yr, 70% after 5 yr
Adefovir	0% after 1 yr. ~30% after 5 yr
Entecavir	0% after 1 yr, ~1% after 2 & 3 yr
Telbivudine	6-12% after 1 yr
Lam-experienced pts	
Adefovir	~20% after 2 yr
Entecavir	1%, 9%, ~17% after 1, 2 & 3 yr

Predictors of Sustained Response

HBeAg + CHB: HBeAg seroconversion

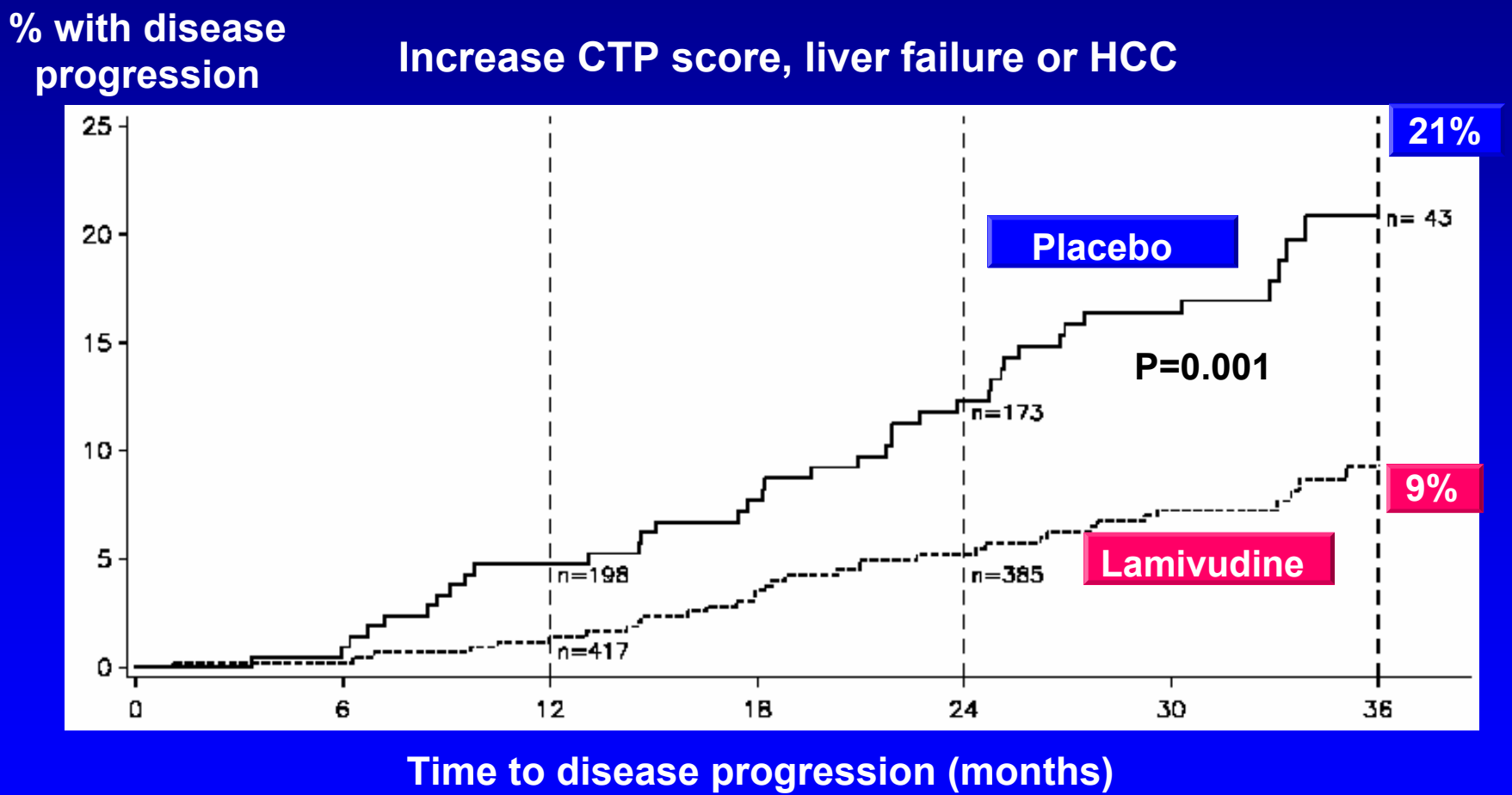
- High pre-treatment ALT or histologic activity index
- Low serum HBV DNA
- HBV genotype A +/- B (IFN)

HBeAg – CHB: Sustained suppression of serum HBV DNA

- ???

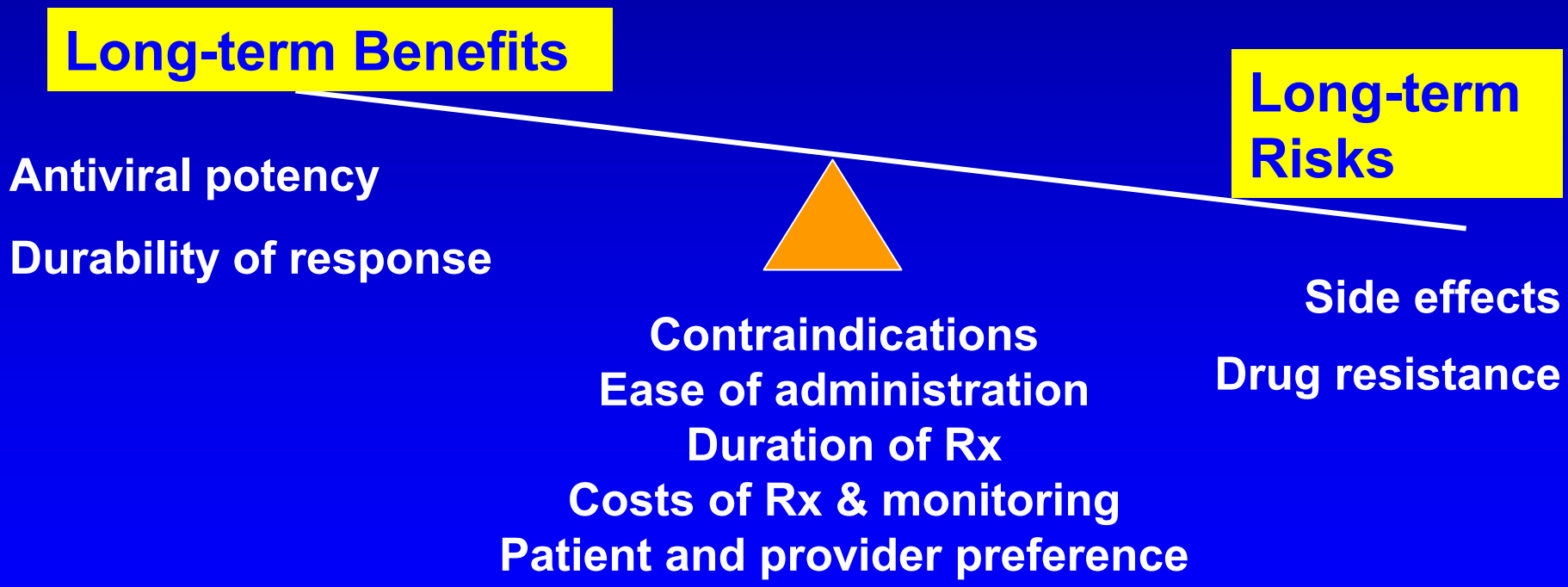
Antiviral Therapy Prevents Disease Progression

Bridging fibrosis or cirrhosis, HBeAg+ / HBV DNA >700,000 GEq/ml



Liaw YF, NEJM 2004; 351:1521

What should be the primary treatment?



When can treatment be stopped?

- **IFN / Peg IFN: fixed duration, 12 mos**
  - HBeAg+, sustained HBeAg seroconversion ~30%
  - HBeAg-, sustained viral suppression ~20%
- **Nucleos(t)ide analogues: until endpoint is achieved**
  - HBeAg+ pts: HBeAg seroconversion + ≥6 mos consolidation Rx, ~50% after 5 yr Rx
  - HBeAg- pts: HBsAg loss, ~5% after 5 yr Rx
  - Cirrhosis pts: life-long?

Should indication of treatment be based on HBV DNA or ALT?

- Positive HBeAg and high serum HBV DNA have been reported to be associated with increased risk of cirrhosis and HCC
  - Data based on a single HBV DNA value, in patients with perinatally acquired HBV infection who were >40 yrs old at enrollment
- Patients with normal ALT may have inflammation and even cirrhosis on biopsy and patients with ALT 0.5-1x ULN have increased risk of hepatic complications and liver related deaths vs. those with ALT <0.5x ULN
  - Predictors of abnormal histology: age >40, HBeAg-, ALT intermittently abnormal or close to ULN
  - Can assessment at 1 time point predict prognosis of patients with chronic HBV infection? Should decisions on long-term treatment be based on a single assessment?

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Other Hepatitis B Medications

Interferon-alpha (Intron A, 1991) is given by injection several times a week for six months to a year, or sometimes longer. The drug can cause side effects such as flu-like symptoms, depression, and headaches.

Pegylated Interferon (Pegasys, 2005) is given by injection once a week usually for six months to a year. The drug can cause side effects such as flu-like symptoms, depression and other mental health problems. adults.

Lamivudine (Epivir-HBV, Zeffix, or Heptodin, 1998) is a pill that is taken once a day, with almost no side effects, for at least one year or longer. The possible development of hepatitis B virus mutants during and after treatment is a concern. Both children and adults.

Adefovir dipivoxil (Hepsera, 2002) is a pill taken once a day, with few side effects, for at least one year or longer. Kidney problems can occur while taking the drug and is a concern, but are reversible once the drug is stopped. adults. Pediatric clinical trials are being planned.

Entecavir (Baraclude, 2005) is a pill taken once a day, with almost no side effects for up to one year. It is considered to be the most potent oral antiviral drug for chronic hepatitis B to date. adults. Pediatric clinical trials may be planned.

Telbivudine (Tyzeka, Sebivo, 2006) is a pill taken once a day, with almost no side effects for up to one year. Studies have shown that it rapidly and profoundly suppresses HBV levels. adults.